# The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review

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## Abstract

**Context**. Controversy exists regarding the therapeutic role of pelvic lymph node dissection (PLND) in patients undergoing radical prostatectomy for prostate cancer.

**Objective**. To systematically review the relevant literature assessing the relative benefits and harms of PLND on oncological and non-oncological outcomes in patients undergoing radical prostatectomy for prostate cancer.

**Evidence acquisition**. Medline, Medline In-Process, Embase, and the Cochrane Central Register of Controlled Trials were searched up to December 2015. Comparative studies evaluating no PLND, limited, standard, and (super)-extended PLND and reporting on oncological and non-oncological outcomes were included. Risk-of-bias and confounding assessments were performed. A narrative synthesis was undertaken.

**Evidence synthesis**. Overall, 66 studies recruiting a total of 275,269 patients were included (44 full-text articles and 22 conference abstracts). Oncological outcomes were addressed by 29 studies, one of which was a randomized clinical trial (RCT). Non-oncological outcomes were addressed by 43 studies, three of which were RCTs. There were high risks of bias and confounding across most studies. Conflicting results emerged when comparing biochemical and clinical recurrence, while no significant differences were observed among groups for survival. Conversely, the majority of studies showed that the more extensive the PLND, the greater the adverse outcomes in terms of operating time, blood loss, length of stay and post-operative complications. No significant differences were observed in terms of urinary continence and erectile function recovery.

**Conclusion**. Although representing the most accurate staging procedure, PLND and its extension are associated with worse intra-operative and peri-operative outcomes, whereas a direct therapeutic effect is still not evident from the current literature. The current poor quality of evidence indicates the need for robust and adequately powered clinical trials.

**Patient summary**. Based on a comprehensive review of the literature, this article summarises the benefits and harms of removing lymph nodes during surgery to remove the prostate for cancer. Although the quality of the data from studies was poor, the review suggests lymph node removal may not have any direct benefit on cancer outcomes and may instead result in more complications. Nevertheless, the procedure is still justified because it enables accurate assessment of cancer spread.

## 1. Introduction

The current EAU prostate cancer (PCa) guidelines recommend performing extended pelvic lymph node dissection (PLND) in high-risk and intermediate-risk patients when the estimated risk for positive lymph nodes exceeds 5% [1]. However, the therapeutic role of PLND during radical prostatectomy for the management of PCa remains controversial. There are reports suggesting that PLND results in improved pathological staging, and that extending the PLND template may increase its staging accuracy. Nevertheless, the oncological benefit of the procedure is still unclear [2].

Historically, the decision to perform a PLND, and on how extensive it ought to be, has been left to the clinical judgment of the surgeon. The lack of clarity regarding the oncological benefit of performing a PLND and the lack of standardised definitions and terminologies regarding the PLND template have led to a wide variety of "experience-based approaches" [3,4], which render any comparisons between them difficult and fraught with uncertainties. It is also unclear whether the PLND outcomes vary between different patient subgroups (i.e. low- vs. intermediate- vs. high-risk localised disease). Furthermore, a PLND may be associated with an increased risk of adverse events, morbidity, length of stay and healthcare costs. However, the assertion that a more extensive PLND leads to higher complication rates has not always been confirmed [5-7].

The objective of this systematic review was to evaluate the benefits and harms of PLND, incorporating the comparison between the different PLND extents (i.e. no PLND, limited PLND, standard PLND, extended PLND and super-extended PLND) during radical prostatectomy for PCa, and to identify which patients benefit most from PLND.

## 2. Evidence acquisition

### *2.1 Search strategy, selection of studies, and data extraction*

The protocol for this review has been published (http://www.crd.york.ac.uk/PROSPERO; registration number CRD42015024848), and the search strategy is outlined in ***Appendix 1***. Briefly, databases including MEDLINE, Embase and Cochrane Central Register of Controlled Trials were systematically searched. Only English language articles and studies published from January 1980 to December 2015 were included. The search was complemented by additional sources, including the reference lists of included studies. Two reviewers (NF and PPW) screened all abstracts and full-text articles independently. Disagreement was resolved by discussion or reference to an independent third party (TVdB and SJ). The review was commissioned and undertaken by the EAU Prostate Cancer Guideline Panel as part of its guideline update for 2017.

### *2.2 Types of study designs included*

All comparative studies (i.e. randomised controlled trials [RCT] and non-randomised comparative studies [NRCS]) with at least one experimental arm and one control arm were included. Studies with more than two arms were also included. Single-arm case series, case reports, commentaries, reviews and editorial commentaries were excluded. Relevant systematic reviews were scrutinised for potentially relevant studies for inclusion. Studies available as non-full text articles only (e.g. conference abstracts) were eligible for inclusion.

### *2.3 Types of participants included*

The study population was limited to men above the age of 18 years with histologically proven T1-3 N0 M0 PCa according to the TNM staging system (all versions of the TNM staging system) and who were undergoing radical prostatectomy. Patients with cNx or cMx were accepted for low- and intermediate-risk localised disease. Men with localised disease were further stratified according to the D'Amico classification, if data were available.

### *2.4 Types of interventions included*

The interventions were PLND performed during radical prostatectomy, incorporating all approaches (including open, robotic, or laparoscopic) and the different extents. Due to the expected heterogeneity in defining the extent of PLND across studies, for the purpose of standardisation, the extent of PLND was determined *a priori* based on discussion and consultation with a reference expert panel (EAU Prostate Cancer Guideline Panel) and was categorized as follows (***Figure 1***): (1) No PLND; (2) Limited PLND (lPLND): obturator nodes; (3) Standard PLND (sPLND): obturator and external iliac nodes; (4) Extended PLND (ePLND): obturator, external, and internal iliac nodes; (5) Super-extended PLND (sePLND): ePLND + common iliac, pre-sacral, and/or other nodes; and (6) PLND extent undefined or unclassified. Studies reporting discrepant extents and definitions were reclassified according to the above definitions.

### *2.5 Type of outcome measures included*

The primary outcomes were biochemical recurrence (BCR), clinical recurrence (i.e. development of distant metastasis), cancer-specific survival and overall survival. Secondary outcomes included adverse events or complications reported either as grade of severity (e.g. Clavien) or individual rates, intra-operative and post-operative

outcomes including operative time, blood loss, blood transfusion, duration of hospital stay, 30-day readmission rate, 90-day mortality, and functional outcomes including urinary continence and erectile function recovery. Lastly, data regarding the median total number of lymph nodes retrieved and total number of positive lymph nodes in relation to the extent of PLND were also extracted.

### *2.6 Assessment of risk of bias*

The risk of bias (RoB) of RCTs was assessed using the standard Cochrane RoB assessment tool for RCTs, whilst the RoB for NRCS was assessed using the modified Cochrane tool that included additional items to assess confounding bias. This was a pragmatic approach informed by the methodological literature pertaining to assessing RoB in NRCS [8]. A list of important outcome-specific prognostic confounders was defined *a priori* by the EAU PCa guideline panel: clinical stage, pathological stage, pathological Gleason score and adjuvant treatment for oncological outcomes; and age, BMI, performance status and surgical route for non-oncological outcomes. The overall judgement regarding each confounder was based on whether it was measured, if it was balanced across groups and whether any statistical adjustment was made.

### *2.7 Data analysis*

A data extraction form was developed to collect information on study design, participant characteristics, characteristics of interventions, and outcome measures. Two reviewers (NF and PPW) independently extracted data relating to the pre-specified outcomes. Descriptive statistics were used to summarise baseline characteristics data. For time-to-event data (e.g. survival analysis), estimates such as median survival or the percentage event-free (survival rate) at specific time points as

reported by authors were extracted. Adjusted and unadjusted hazard ratios (HR) to estimate the size of intervention differences were extracted if available. For categorical data, point estimates reported as proportions (%), risk ratios (RR) and odds ratios (OR) were extracted. For continuous outcomes, mean difference (MD) with corresponding 95% confidence intervals (CI) were extracted. For NRCS, a narrative synthesis of the data was planned. Where possible, dichotomous outcomes comparing the intervention effect were analysed using RR with 95% CI. Means and standard deviations were used to summarise the continuous outcome data and compared using MD and 95% CI.

To explore the potential impact of clinical heterogeneity on outcomes, subgroup and sensitivity analyses were planned on the following variables: age, PSA level, and type, schedule and timing (early vs. deferred) of androgen deprivation therapy.

## 3. Evidence Synthesis

### *3.1 Quantity of evidence identified*

The study selection process is outlined in the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flow diagram (***Figure 2***). In total, 4,377 records were identified through database searching, and 3,840 were screened after duplicates removal. Of these, 178 articles were eligible for full-text screening, and 139 conference abstracts were assessed for eligibility. Finally, 66 studies recruiting a total of 275,269 patients met the inclusion criteria (44 full-text papers and 22 conference abstracts, with each reporting on a separate study).

### *3.2 Characteristics of the included studies*

Data were included from 66 studies, three of which were RCTs [9-11], four were prospective NRCS [12-15], and the rest were retrospective NRCS [16-74]. The baseline characteristics for all included studies addressing oncological and non-oncological outcomes are shown in ***Table 1*** and ***Table 2***, respectively. The template and extents of PLND performed in the included studies are summarised in ***Supplementary Table***: the more extensive the PLND, the higher the rate of pN1 disease.

#### *3.2.1 Characteristics of studies reporting on oncological outcomes*

Baseline characteristics of studies evaluating oncological outcomes are summarized in ***Table 1***. Overall, 29 studies were included. Specifically, 21 studies (15 full-text articles and 6 conference abstracts) compared no PLND vs. any form of PLND, whereas 8 studies (4 full-text articles and 4 conference abstracts) compared lPLND or sPLND vs. ePLND or sePLND.

*3.2.2 Characteristics of studies reporting on non-oncological outcomes*

Baseline characteristics of studies evaluating non-oncological outcomes are summarized in ***Table 2***. Overall, 43 studies were included. Specifically, 25 studies (18 full-text articles and 7 conference abstracts) compared no PLND vs. any form of PLND, whilst 18 studies (12 full-text articles and 6 conference abstracts) compared lPLND or sPLND vs. ePLND or sePLND.

## 3.3 Risk of bias and confounding assessment of the included studies

Risk of bias and confounding assessment for each of the individual studies were performed, and the results are presented in ***Figure 3a*** (studies reporting on oncological outcomes) and ***Figure 3b*** (studies reporting on non-oncological outcomes). There was high or unclear RoB across most domains. However, some confounding factors were adequately considered through statistical adjustment in a significant proportion of studies, including stage and pathological Gleason score for studies reporting oncological outcomes (***Figure 4a***), and age and BMI for studies reporting on non-oncological outcomes (***Figure 4b***).

## *3.4 Comparisons of interventions results*

### *3.4.1 Oncological outcomes*

*3.4.1.1 No PLND vs. any form of PLND*

Overall, 21 retrospective comparative studies (15 full-text articles and 6 conference abstracts) compared no PLND vs. any form of PLND for oncological outcomes (**Table 3a**). No RCTs were identified for this comparison.

*Biochemical recurrence*

Biochemical recurrence was evaluated in 18 studies, in which 5/18 [28%] involved lPLND, 1/18 [5%] sPLND, 3/18 [17%] ePLND, and 9/18 [50%] undefined PLND. Out of these, 16 did not find any statistically significant difference between the two groups [16-18,21,23-25,27-31,33-36]. This negative finding also applied to the various sub-groups of patients (e.g. low-risk disease [23], or pT2, pT3, or pT2 R0 disease [24]). On the other hand, counter-intuitive findings were observed in two different retrospective studies regarding the impact of PLND compared with no PLND on BCR [19,22]. Specifically, *Boehm et al* evaluated a cohort of 11,127 patients, including 6,810 pN0 patients and 4,884 pNx patients treated with radical prostatectomy between 1992 and 2011 [19]. Through multivariable Cox regression analysis, pNx was associated with a lower risk of BCR compared to pN0 (HR: 0.81; 95% CI: 0.72–0.9; $p<0.05$). Despite the use of multivariable analysis, the significant baseline differences between the two groups may explain the higher risk of recurrence among pN0 patients. Furthermore, the extent of PLND was not reported. Conversely, *Liss et al* analysed a cohort of 492 patients treated with robotic assisted radical prostatectomy between 2007 and 2011 [22]; 54 received ePLND, 231 received sPLND, and 207 did not receive any PLND. At a median follow-up of approximately 1 year, BCR was significantly different among the three groups: 30% vs. 15% vs. 3.4%, respectively ($p<0.001$). However, when ePLND was compared with sPLND in high-risk patients only, no significant differences were observed ($p=0.294$).

*Distant metastasis*

Distant metastasis following radical prostatectomy were evaluated by two retrospective studies which reported conflicting results [19,23]. *Mitsuzuka et al* analysed a series of 222 low-risk patients and found a metastasis-free survival of

100% in both sPLND and no PLND groups at a median follow-up of 60 and 26 months, respectively [23]. Conversely, the already mentioned *Boehm et al* study found that no PLND was associated with a lower risk of distant metastasis at multivariable analysis (HR: 0.62; 95 % CI: 0.41, 0.92; p<0.05) [19]. As explained in the previous paragraph, baseline differences among pNx and pN0 patients, and important selection bias may explain this finding.

*Cancer-specific and overall mortality*

Cancer-specific and overall mortality were analysed by 6 studies. Of these, PLND was standard in one study [23], while its extension was not reported in the other five studies [19,20,26,27,32]. None of these studies demonstrated any statistically significant differences in cancer-specific mortality [20,23,26,27,32] and overall mortality [19,23] between PLND and no PLND. Mean follow-up was longer than 3 years in five studies, ranging between 4 [19] and 11 years [32]. One conference abstract by *Pokala et al* did not report information about follow-up [27].

*3.4.1.2 Limited / standard PLND vs. (super)-extended PLND*

Overall, 8 studies (4 full-text articles and 4 conference abstracts) compared limited / standard PLND vs. (super)-extended PLND for oncological outcomes (**Table 3b**). One study was a RCT [9].

*Biochemical recurrence*

Biochemical recurrence was evaluated by all 8 studies, and conflicting results were observed. In the RCT by *Lestingi et al* which was reported as a conference abstract only, there was no significant difference in terms of BCR between lPLND and ePLND (p=0.39) at a median follow-up of 14.4 and 13.4 months, respectively [9].

Similarly, ePLND did not alter BCR rates at a median follow-up of 36 months in a retrospective study by *Kim et al* [40]. Furthermore, ePLND did not provide better biochemical outcome in four comparative studies [39,41,42]. However, all these studies were retrospective in design, and three of them were conference abstracts. Two additional studies did showed a statistically significant benefit of ePLND over limited/standard PLND but only in specific sub-groups of patients: intermediate-risk patients (96% vs. 90%; p=0.017) [38], and pN1 patients with <15% of retrieved nodes affected (43% vs. 10%; p=0.01) [43]. However, counter-intuitive findings were observed in a retrospective study where ePLND was associated with higher risk of 7-year BCR compared with lPLND in pT2 patients only (5% vs. 0%; p=0.01) [37]. This result may reflect the selection bias of the study, as surgeons tended to perform more extensive nodal dissection in higher risk patients.

*Distant metastasis*

No studies reported on distant metastasis outcome.

*Cancer-specific and overall mortality*

Cancer-specific mortality was reported in one conference abstract [41] that showed that ePLND did not provide a statistically significant survival benefit over sPLND (p>0.05). However, the median follow-up was 34 months, presumably too short for addressing survival outcomes of prostate cancer.

### *3.4.2 Non-oncological outcomes*

*3.4.2.1 No PLND vs. any form of PLND*

Overall, 25 retrospective comparative studies (18 full-text articles and 7 conference abstracts) compared no PLND vs. any form of PLND for non-oncological outcomes (**Table 4a**).

*Intra-operative and peri-operative outcomes*

Data was obtained from 20 retrospective studies regarding operative time, blood loss, and post-operative complications [12,15,19,22,45,48-50,52-63]. Mainly, PLND was associated with a significantly higher risk of lymphocele in the majority of studies that addressed the outcome (12/16 studies). Moreover, a population-based study showed a higher 90-day mortality rate in the PLND group (0.29% vs. 0.20% in case of open surgery and 0.29% vs. 0.13% in case of robotic surgery) without statistical significance being reported by this conference abstract [46]. Conversely, a single institution study did not find any significant difference at multivariable analysis for 30-day readmission rates between the two groups, after adjusting for age at surgery, Charlson comorbidity index, and post-operative complications (OR not reported; p>0.1) [47].

*Functional outcomes*

Three retrospective studies did not find any significant differences between PLND and no PLND regarding urinary continence (OR not reported) [13] and erectile function recovery (OR: 0.95; 95% CI: 0.63, 1.43; p=0.8; and HR: 0.9; p=0.8) [44,51].

*3.4.2.2 Limited / standard PLND vs. (super)-extended PLND*

Overall, 18 studies (12 full-text articles and 6 conference abstracts) compared limited / standard PLND vs. (super)-extended PLND for non-oncological outcomes (**Table 4b**). Three were RCTs [9-11].

*Intra-operative and peri-operative outcomes*

In comparing lPLND vs. ePLND, one RCT recruited 226 patients with intermediate-risk disease [9], and another RCT recruited 234 patients with high-risk disease [10]. In the study by *Lestingi et al*, ePLND was associated with statistically significant increases in operative time, intra-operative complications, bleeding, and hospital stay ($p<0.001$), but not with post-operative complications according to the Clavien-Dindo scale ($p=0.12$). Further details were not reported by the conference abstract [9]. Similarly, in the study by *Schwerfeld-Bohr et al*, ePLND prolonged surgical time by 30 minutes compared with lPLND. In this study, lymphocele development was the only complication which occurred significantly more often after the extended procedure compared with limited PLND (17% vs. 8%) [10]. In another RCT, 123 patients were randomized to either ePLND on the right hemi-pelvis versus lPLND on the left hemi-pelvis. Complications including lymphocele (3% vs. 1%) and lower extremity oedema (3% vs. 2%) occurred more commonly on the side which underwent ePLND compared with lPLND [11].

When considering data from 15 retrospective studies, conflicting results were observed. Five studies showed significantly higher intra-operative and post-operative complications in the ePLND group compared with lPLND / sPLND [14,40,70-72], while five studies did not show any statistically significant differences [42,64,66-68]. Similarly, the rate of lymphocele was significantly higher in the ePLND group in four studies [40,70,73,74], while no significant differences were observed in four others [42,64,66,67].

*Functional outcomes*

One retrospective comparative study did not find any significant differences regarding urinary continence (HR: 1.07; 95% CI: 0.87, 1.31; p=0.5) and erectile function recovery (HR: 1.11; 95% CI: 0.75, 1.63; p=0.6) between ePLND and lPLND [37].

## 4. Discussion

To date, PLND represents the most accurate staging procedure to assess the presence of lymph node metastasis in PCa patients [2,75]. However, its therapeutic role from an oncological effectiveness perspective remains unclear. The objectives of this systematic review were to determine the benefits and harms of PLND during radical prostatectomy compared with no PLND, how the different extents of PLND compare with one another, and which patients benefit most from PLND.

### *4.1 Principal findings*

This systematic review, after screening almost 4,000 articles, highlighted important results that deserve attention. Firstly, the overall quality of evidence based on study design and RoB assessment of included studies was low, with most studies judged to be at moderate to high risk of bias. Indeed, out of 67 included studies, only three were RCTs, and four were prospective NRCS, while the rest were retrospective NRCS. Furthermore, anatomical extents of PLND was not specified in more than half of the included studies, highlighting a lack of standardised definitions for extent of PLND in the current literature.

Secondly, when considering oncological outcomes, there was no good quality evidence indicating that any form of PLND improves outcomes compared with no PLND. Out of 21 studies, all of which were retrospective in nature, none showed statistically significant differences in favour of PLND when compared with no PLND for BCR, distant metastasis, or survival. Similarly, no good quality evidence was retrieved indicating that ePLND improves oncological outcomes compared with lPLND or sPLND. Data from 13 studies, one of which was a RCT reported as a conference abstract, showed conflicting results; 2 studies (including the RCT)

showed no differences in BCR at short-term follow-up; 2 studies showed no differences in BCR between the interventions for the entire cohort, but found that only certain subgroups of patients benefited from an ePLND compared with lPLND / sPLND for BCR; and 9 studies found no significant differences in BCR.

Finally, considering non-oncological outcomes, PLND was associated with significantly worse intra-operative and peri-operative outcomes compared with no PLND in 20 retrospective studies. Functional outcomes including urinary continence and erectile function recovery were evaluated in three retrospective studies and no significant differences were observed. Similar results were obtained when comparing lPLND or sPLND with ePLND in 18 studies.

Based on current results, the therapeutic benefits of PLND during radical prostatectomy remain unproven. However, two important factors need to be considered:

1) PLND may in theory be curative for selected patients, with limited nodal involvement entirely removed at the time of surgery (*direct effect*). In support of this, a recent retrospective study showed that biochemical relapse is likely in patients with limited nodal disease after radical prostatectomy and PLND, however, clinical progression was observed in less than 50% of them [76]. Furthermore, an additional retrospective study showed that the removal of a higher number of lymph nodes in pN1 patients was associated with improvement in cancer-specific survival rate [77]. However, such hypotheses still need to be verified by level-1 evidence studies.

2) PLND may represent a stratification tool to identify patients who benefit from adjuvant treatments that improve survival outcomes (*indirect effect*). As an example, *Abdollah et al* recently identified specific categories of pN1 patients who

benefited from adjuvant radiation therapy combined with adjuvant hormonal therapy [78]. Therefore, more comprehensive an accurate nodal staging through ePLND may indirectly improve pN1 patient prognosis.

### *4.2 Implications for clinical practice*

The current EAU prostate cancer guidelines recommend performing ePLND in high-risk and intermediate-risk patients for staging if the estimated risk for positive lymph nodes exceeds 5%, and avoiding PLND in low-risk patients. Bearing in mind the low quality of evidence for PLND outcomes from published data, the cautious EAU guidelines statement concerning PLND for treatment is supported by these current findings.

Indeed, PLND during radical prostatectomy should not be performed in all patients because of the lack of solid evidence on its oncological benefit and because of the harms that are associated with it. On the other hand, it is equally important not to blindly omit PLND in all patients either for exactly the same reason, which is the lack of solid evidence disproving its oncological benefit.

Because an increasing PLND extent improves nodal staging of patients [2,79], it is advisable to always perform an ePLND whenever PLND is indicated. However, ePLND should be avoided when the harms are expected to exceed its possible benefits. Predictive models assessing the risk of lymph node metastasis represent the best available tool to help facilitate decision-making.

### *4.3 Implications for further research*

The current poor quality of evidence indicates the need for robust and adequately powered clinical trials with appropriate controls, using standardised

template definitions, standard operating procedures for pathological work-up, and adequate duration of follow-up in order to determine its therapeutic effectiveness based on oncological outcomes. Results from two on-going prospective studies may improve the level of evidence in the future (NCT01812902, NCT01555086). However, three main factors should be considered when evaluating a RCT in this field:

1. The tumour: tumour risk scoring is a fundamental step for the study design and populations with higher risks of lymph node disease should be investigated. As an example, a PLND would be unlikely to have a significant effect when performed in a population of low-risk patients. Therefore, judicious patient selection is mandatory.

2. The PLND procedure: the definition and extent of PLND represent other important factors to be considered. Indeed, even if ePLND has shown a superior diagnostic accuracy compared to lPLND, it is unlikely to detect all positive lymph nodes [80]. Furthermore, several surgeon-related factors may importantly influence the final results. As an example, in the SEAL AUO AP 55/09 trial [10] the observed rate of pN1 disease in the ePLND and lPLND group was 15% and 12%, This finding suggests a surgeon-related bias towards more meticulous PLND in the limited group. Therefore, predefined templates should be designed and respected in future studies.

3. The pathological examination: pathological evaluation of pelvic lymph nodes remains controversial, with a lack of consensus on the specimen processing and identification of nodes, and heterogeneity in terms of definitions, thresholds, and reporting. Indeed, there is evidence that both the surgeon and the pathologist may influence the number of lymph nodes removed and the number of positive nodes at final pathology [81,82]. Therefore, standard-operating procedures for pathological work-up should be predefined in future studies.

In view of the fact that PLND is a morbid procedure which leads to a higher risk of complications, there is a need to consider alternative nodal staging methods, such as sentinel node biopsy [83].

### *4.4 Limitations and strengths*

The current study represents the first systematic review addressing benefits and harms of different anatomical extents of PLND during radical prostatectomy. The review elements were developed in conjunction with a multidisciplinary panel of content experts (EAU Prostate Cancer Guideline Panel), which included a patient representative, and the review was performed robustly in accordance with recognised standards. Limitations include the relatively low quality of the evidence base, with the majority of studies being judged to have moderate to high risk of bias in most domains, especially in relation to oncological outcomes. There was also significant clinical and methodological heterogeneity across studies, with different definitions and thresholds used in terms of describing the PLND procedure. In many instances, the extent of PLND was not described in detail, which made data acquisition, analysis and interpretation difficult. Finally, the so-called *Will Rogers phenomenon* should also be taken into account. As an example, in studies focused on pN0 patients, those who received more extensive PLND were better staged and, thus, were more likely to be really free from LNI. Conversely, pN0 patients with a lower number of removed lymph nodes were less accurately staged. The less favourable survival rates observed in these individuals may largely be related to this phenomenon. Such limitations indicate that the findings of the review should be interpreted within the appropriate context.

## 5. Conclusion

The majority of studies showed that PLND and its extensions are associated with worse intra-operative and peri-operative outcomes, whereas a direct therapeutic effect is still not evident from the current literature. The current poor quality of evidence indicates the need for robust and adequately powered clinical trials. In the meantime, because of its recognised staging benefits, extended PLND should be undertaken whenever PLND is indicated in appropriate patients, judiciously selected based on a risk-stratified approach.

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